15.0 AMYOTROPHIC LATERAL SCLEROSIS (ALS)

STATEMENT TO THE PUBLIC

Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease)

The reviewers used two distinct sets of guidelines to evaluate the evidence:

- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence as "Inadequate" to reach a conclusion.*

- *Using the guidelines developed especially for the California EMF Program they concluded that it is "50% to 90% likely" that exposure to EMFs at home or work could add slightly to an individual's ordinarily low lifetime risk of contracting Lou Gehrig's disease. As this phrase implies, there is also a chance that EMF has no effect on this risk at all. However if EMFs really contribute to this condition, even this slight added lifetime risk could be of concern to regulators because health protective regulations are already controlling agents that are thought to convey even lower added lifetime risks.*

15.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

FIGURE 15.1

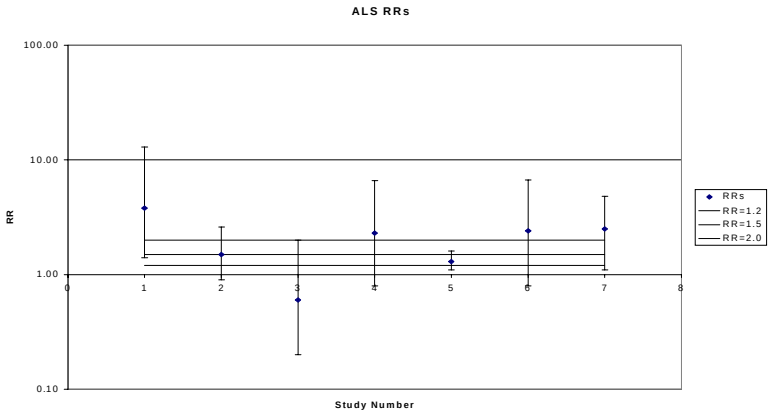

Figure 15.1 and Table 15.1 display the seven studies which deal with electrical occupation or estimated magnetic field exposure and the occurrence of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's Disease). The graph shows the relative risks reported in the seven studies. Ahlbom (2001) calculated the meta-analytic summary relative risks for all seven, the clinic-based studies, the mortality-based studies, and the two utility cohort studies that assigned magnetic field exposure based on a job-activity matrix. For all seven studies the meta-analytic summary RR was 1.5 (1.2-1.7); for the two utility cohort studies it was 2.7 (1.4-5.0). Thus, the evidence suggests an association between ALS and working in an electric occupation or having a job with a high magnetic field exposure within a utility company. Six of seven studies report RR above 1.0 (P =.055). Given the small number of studies, the fact that 86% of the relative risks are above 1.0 does not achieve conventional statistical significance.

TABLE 15.1

	REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
1.	(Deapen and Henderson 1986)	Study population: not specified. Cases: ALS society, USA, in 1979. Controls: friends.	Questionnaire: electrical occupation 3 yr prior to diagnosis.	CC	678 cases (19 electr. occ.) 518 controls (5 electr. occ.)	3.8 1.4-13.0
2.	(Gunnarsson 1991)	Male population of Sweden, 1970-83. Cases: deaths with ALS as underlying or contributing cause in mortality registry. Controls: random sample from population.	Job title in 1960 census: electricity worker.	CC	1067 cases (32 exposed) 1005 controls	1.5 0.9-2.6
3.	(Gunnarsson 1992)	Male population of central and southern Sweden in 1990. Cases: patients with MND in neurological departments. Controls: random sample from population.	Questionnaire: electricity work and exposure to MF.	CC	58 cases (4 MF exposure) 189 controls	0.6 (MF exp.) 0.2-2.0
4.	(Davanipour, Sobel et al. 1997)	Study base: not specified. Cases: ALS patients at outpatient clinic in Southern California. Controls: relatives.	Questionnaire about occupational history: EMF exposure assessed by hygienist. Cumulative (E1) and average (E2) exposure.	CC	28 cases 32 controls cut off: 75th percentile of case distribution	2.3 0.8-6.6 average (E2)
5.	(Savitz, Loomis et al. 1998)	Male population in 25 states, US, 1985-91. Cases: deaths from ALS. Controls: deaths from other causes.	Job title on death certificate: electrical occupation in aggregate and individual jobs.	CC	114 cases in electr. occ. in aggregate	1.3 1.1-1.6
6.	(Savitz, Checkoway et al. 1998)	Male employees at 5 US utility companies, 1950-1988. Cases: deaths with ALS mentioned on death certificate, identified through multiple tracking sources.	Measurements and employment records. Combination of duration and EMF index.	Cohort	9 cases with > 20 years in exposed occ.	2.4 0.8-6.7
7.	(Johansen 1998)	Male employees in Danish utility companies observed during 1974-1993. Cases: deaths from ALS in mortality registry.	Employment records and JEM: estimated average exposure level.	Cohort	21236 males in cohort. 14 (9 exposed) cases	2.5 1.1-4.8

15.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 15.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations are above 1.00 or statistically significant.	(F1) The narrow confidence limits in the meta-analytic summaries and the low likelihood of this pattern of evidence by chance leans away from chance as an explanation.	(C1) A non-chance explanation must be sought.

TABLE 15.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The case control studies are subject to recall bias. All studies are subject to the authors presenting only the strongest associations of the many generated during analysis.	(F1) Like the electric shock and trauma associations in questionnaire-based case control studies, electrical occupation is subject to recall bias. But two large occupational cohort studies and a case control study, objectively assessing EMF exposure, show a higher ALS rate in association with high EMF work. (F2) If there is any consistent bias, it is non-differential measurement error, which would tend to obscure associations.	(C1) Bias upward is not a big concern in this evidentiary base. Bias downward may be likely.

TABLE 15.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One doubts that electrical occupation or high EMF electrical work is associated with ALS. (A2) If it is, then the association is not due to magnetic fields but to the delayed effect of many shocks experienced in those jobs. Experimental work shows that shocks, not EMF exposure, is responsible for acute vascular trauma. (A3) Kurtzke (1980) and others have shown association between ALS and physical injury occurring many years before. Electrical trauma may also have delayed effects. (A4) Deapen (1986), Gallager (1987), Cruz, (1999) and Savettieri (1991) showed associations between ALS and self-reported electrical shock, often occurring years before. (A5) (Johansen 1998) showed that fatal electric shock was associated with high EMF jobs. (A6) Serious non-lethal shocks should be more common in high EMF jobs also.	(F1) Since high amperage is often associated with high voltage, it is not surprising that high magnetic field jobs would have a higher probability of death among those shocked. It does not follow that the frequency of shocks would be greater. (F2) Kondo (1981) and Gunnarsson (1992) showed weak protective associations with shock. Deapen (1986), Savettieri (1991), and Cruz (1999) were of borderline statistical significance, so by conservative criteria, five out of six studies were null. Four out of six studies had ORs larger than 1.00. (F3) All these studies rely on recall. (F4) The ORs conveyed by shock leading to unconsciousness in Deapen (1986) are 2.8 (1.0-9.9). The ORs conveyed by high EMF work, excluding 3 out of 19 workers with shock, are 3.3 (1.1-10.3). Shock to unconsciousness does not explain the EMF association, unless one postulates that virtually all high EMF workers have received lesser shocks which conveyed more risk than shock to unconsciousness. Cruz (1999) reports a RR = 0.7 (0.5-1.1) from multiple non-injury shocks.	(C1) The evidentiary base to describe the frequency of shocks and link them to EMF exposure in an objective way is non-existent, so any link between magnetic field and shock exposure is speculative. (C2) The reported associations with ALS, based on objective assessments of magnetic field, are of about the same strength as those conveyed by subjectively recalled shock history in the general public. (C3) One would need to believe that virtually all high EMF electrical workers had experienced shocks that rendered them unconscious during their work life or that common minor shocks carry the same risk as major shocks, for shocks to explain the magnetic field association with ALS. This seems implausible on the face of it but needs to be evaluated. (C4) A similar concern as that voiced in C3 would apply to contact currents as a confounder of magnetic fields. (C5) For the same reason, it is also implausible that the history of physical trauma in high EMF workers could explain the association. (C6) The 60-year-old literature, (Alexander 1938) in shock pathology relates to acute, not delayed, effects.

TABLE 15.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The associations are modest and could be due to bias.	(F1) Associations of 2.5 and 3.0 are not so easy to dismiss by invoking bias or confounding.	(C1) We do not put much weight on bias as a default explanation, without specific evidence. (C2) The utility study associations are not so small and are not subject to recall or selection bias. (C3) Exposure misclassification could lead to downward bias.

TABLE 15.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One should only pay attention to statistically significant associations. Of seven studies of electrical work or magnetic field exposure, only three were significant; and the ORs in those studies ranged from 1.3 to 3.8.	(F1) One should look at the general pattern among seven studies. Six reported OR's above 1.00.	(C1) There is a recurrent finding of relative risks moderately above the resolution power of the studies, suggesting an association between electrical work and jobs with high magnetic fields, and the occurrence of ALS.

TABLE 15.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Not all the associations are statistically significant. (A2) Estimates of association vary with no clear central tendency.	(F1) All the studies are compatible with a RR of 1.5. (F2) The small heterogeneity has a reasonable explanation. The studies with the crudest exposure had the lowest RRs; those with the highest propensity to selection bias had the highest RRs. The occupational studies with good exposure assessment had associations in-between, with a pooled RR = 2.7 (1.4-5.0).	(C1) The heterogeneity in the 86% of studies with RRs above 1.0 is not great and has a reasonable explanation.

TABLE 15.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Only three of the seven studies look at magnetic field exposure from job-exposure matrices. (A2) Davanipour (1997) shows no statistically significant associations for the whole group. (A3) Savitz (1998) also shows no statistically significant associations for the future group. (A4) Johansen (1998) shows no statistically significant associations for the entire group. (A5) There is no statistically significant dose response. This should considerably decrease confidence that something about high EMF work (much less the EMF mixture itself) causes ALS.	(F1) All three studies that ranked jobs by exposure show increasing risk with EMF exposure, but confidence intervals are wide. (F2) When Johansen's (1998) upper two categories of exposure are combined, the SMR is 2.5 (1.1-4.8). (F3) For both Davanipour (1997) and Savitz (1998), a stronger dose response is seen in persons who have worked for at least 20 years. The associations (high to low) are, respectively, 5.5 (1.3-22.5) and 2.4 (0.7-8.0).	(C1) The evidentiary base is not voluminous and the sizes of the studies are not sufficient to get a clear picture of dose response, but the pattern of evidence is similar to what one would expect if something about high EMF jobs, held for a long time, caused ALS.

TABLE 15.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Electricity is everywhere, so why have we not seen an obvious epidemic of ALS?	(F1) Both exposures to strong EMF and ALS are rare events. The rate of ALS in the highly exposed group is only a few cases per hundred thousand.	(C1) If real, this would take sophisticated studies to detect a temporal trend and would not be obvious.

TABLE 15.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No evidentiary base.	(A1) No evidentiary base.	(C1) There are no EMF animal bioassays for ALS. (C2) Experiments showing bioeffects at high EMF levels increase somewhat the credibility of EMF effects in general.

TABLE 15.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is neither a known physical induction mechanism, nor a chain of mechanisms leading from exposure to pathology.	(F1) It takes a while to figure out the causal processes underlying observations.	(C1) The lack of a mechanism does not pull confidence down as much as its presence would pull it up.

TABLE 15.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See Generic Issues chapter.		

TABLE 15.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See Generic Issues chapter.		

TABLE 15.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See Generic Issues chapter.		

TABLE 15.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no mechanistic reason to pay attention to associations with other diseases.	(F1) Association with Alzheimer's, depression/suicide, and arrhythmic death suggest neurological effects. (F2) Association with other diseases strengthens confidence in EMF mixture bioeffects.	(C1) The evidence of other associations has some relevance.

TABLE 15.2.15

SUMMARY TABLE FOR ALS			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CONFIDENCE?**
Chance: highly unlikely according to meta-analysis.	Unlikely		A non-chance explanation is needed
Upward bias not suggested. The cohort studies most likely free of bias report RRs of 2.7 (1.4-5.0).	Unlikely	Possible	Slight increase
Confounding by shocks proposed but not highly credible.	More possible	Possible	No impact or slight decrease
Strength of association does not fully exceed plausible bias or confounding.	More possible	Possible	No impact or slight decrease
Consistency of association: 86% of RRs are above 1.0 (probability = .055)	Unlikely	Possible	Increase
Dose response suggestive but not clear.	Possible	More possible	No impact or slight increase
Coherent with national and temporal trend.	Possible	Possible	No impact
Experimental: no EMF bioassays.	NA	NA	No impact
Plausibility: no mechanistic explanation.	Possible	Possible	No impact
No analogy.	Possible	Possible	No impact
Temporality.	NA	NA	No impact
Specificity: effect not restricted to subtype.	Possible	Possible	No impact
Other disease associations.	Possible	More possible	No impact or slight increase

15.3 IARC Classification and Confidence of Causality

15.3.1 Statements of Individual Reviewers

Reviewer 1

Degree of Confidence: The epidemiological studies present a fairly consistent pattern, with six out of seven studies reporting a RR > 1.0. The meta-analysis suggests that these results are not due to chance. It is this reviewer's judgment that the results are not likely to be due to bias or confounding, given the diversity of the studies' populations and design. The credibility of the hypothesis of hazard is boosted by the high degree of confidence attributed to other associations and the weakness of the arguments for an alternative explanation. In this reviewer's judgment, an appropriate evaluation is "more than 50% possible." For decision analysis purposes, the reviewer would use values between 30 and 90%, with a median of 60%.

IARC Classification: "possible human hazard".

Reviewer 2

Degree of Confidence: An association somewhat above the resolution power of the studies, which shows up with moderate consistency in studies with and without the likelihood of upward bias and without an obvious confounder, pulls up one's initial degree of confidence quite a bit, despite the lack of analogous agents and a biological explanation. To give credence to the possibility of shocks or contact currents as the true agent to explain this association would require that the association with magnetic field exposure be quite strong and that these shocks be known to produce a larger association with ALS than do magnetic fields. The evidence for either of these assertions is weak to absent. This reviewer would characterize the degree of confidence as "more than 50% possible." For the purposes of the decision model, the reviewer would assign a median degree of confidence, 60%, ranging from 20% to 75%.

IARC Classification: An IARC classification of "possible cause" would be warranted by the fairly consistent epidemiological studies, tempered by the residual uncertainty as to whether magnetic fields are the responsible agent and the lack of animal models or mechanistic explanations of the phenomenon. One could argue that the two utility cohort studies provide confirmation of the Deapen (1986) and Davanipour (1997) and Savitz (1998a) death certificate studies that something about electrical occupations conveys risk—much in the way that the IARC sometimes lists occupation in an industry as a cause for cancer—and that the occupation (as opposed to magnetic fields in the occupations) warrants a "probable human hazard" classification, on the basis of consistent but "limited epidemiological evidence in humans."

Reviewer 3

Degree of Confidence: The human evidence of the ALS studies is based on seven occupational studies that differ considerably in design. This reviewer's posterior is increased over the prior due to the consistent associations, mostly above a RR of 1.0. However, the posterior is slightly decreased by a lack of a dose response and the fact that confounding and bias cannot be ruled out. Hence, the posterior degree of confidence for purposes of the policy analysis falls within the "more than 50% likely" category, with median of 55% and a range of 25% to 80%.

IARC Classification: The human evidence is weak to modest, but still consistent with a low probability of chance explaining the body of evidence. Bias and confounding cannot be ruled out. Also, the animal evidence is inadequate and there is no sound mechanistic rationale. Given this, the evidence as a whole is sufficient for a classification of "possible human hazard."

15.3.2 SUMMARY OF THE THREE REVIEWER'S CLASSIFICATIONS

CONDITION	REVIEWER	IARC CLASS	CONFIDENCE IN CAUSALITY	DEGREE OF CONFIDENCE IN CAUSALITY FOR POLICY ANALYSIS
ALS				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	Possible	> 50% possible	X
	2	Possible	> 50% possible	X
	3	Possible	> 50% possible	X

15.4 QUESTIONS RELEVANT TO DOSE AND THE STAE OF THE SCIENCE

TABLE 15.4.1

HOW CONFIDENT ARE WE THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(A1) No evidentiary base.	(I1) No impact.

TABLE 15.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Davanipour (1997) and Savitz (1998) show an upward trend in risks with microtesla-years with no threshold or plateau in those with 20 or more years of work. Johansen (1998) shows the same for all workers. (C2) Only 3 studies are relevant. No suggestion of threshold or plateau.	(I1) Cannot provide "safe" dose or much dose-response information

TABLE 15.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) No evidentiary base. Primarily daytime, long-term exposure.	(I1) None

TABLE 15.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) To the extent there is any evidence (Savitz and Davanipour), it suggests an interval between exposure and disease around 20 years, the kind of interval seen in studies of the delayed effect of trauma and not the shorter intervals claimed for cancer induction in EMFs. (C2) Not all disease processes initiated by EMFs need to have the same induction period.	(I1) None

TABLE 15.4.5

EMF COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Similar to other reported associations (McGuire 1997) as to size and frequency of occurrence. Not really relevant anyway.	(I1) None

TABLE 15.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) With annual mortality of 1/100,000 (Kurtzke 1980) and RR of 2.7, the 40-year added risk in workers, if real, might not reach the 1/1000 benchmark, but would exceed the 1/100,000 environmental *de minimis* bench mark.	(I1) Could be of environmental regulatory interest, but might be considered *de minimis* from an occupational regulatory point of view.

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TABLE 15.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	(I1) none

TABLE 15.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(F1) There are no known confounders which were not dealt with or which are credible alternative explanations in the cohort studies. These are sophisticated occupational studies and they agree with the case control studies. (C1) The case control studies leave a lot to be desired, but the cohort studies are sophisticated and of good quality. Future study could explicitly deal with shocks and trauma and their association with EMF exposure, and with a more modern approach to the histopathology of major and minor shocks.	(I1) While ALS is so rare that it is probably a *de minimis* risk from a regulatory point of view, a JEM exposure study could address the shock and contact-current hypotheses for this and other diseases. A mechanistic understanding of this association might be relevant to the association with other diseases.

TABLE 15.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO CHANGE ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A population case control study by Nelson et al. will be looking at electric shocks but not EMFs per se. (C2) An incidence study of ALS and EMFs by Johansen is pending.	(I1) Not likely to change assessment.

TABLE 15.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A better JEM exposure study in electrical workers and in the general population could address the hypothesis that contact currents or small shocks are correlated with measured magnetic fields. This could lead to reanalysis of other studies and suggest exposure conditions for experimental studies. The association between EMFs and ALS is unlikely to be explained in one or two iterations of study.	(I1) Results of initial research would be needed to anticipate progress. Current assessment is likely to remain for at least a decade.

15.5 CONCLUSIONS ABOUT DOSE AND THE STATE OF THE SCIENCE

15.5.1 DOSE RESPONSE

Something about electrical occupations, and the aspects of those occupations that are associated with magnetic fields, is associated with ALS. Shocks have been proposed as an explanation, and contact currents could also be invoked although there is no direct evidentiary basis for associating shocks, contact currents, and magnetic fields. Other aspects or non-TWA summary exposure metrics have not be invoked as an explanation. Decades of exposure with a long induction period may be important. The evidentiary base is not present to discuss thresholds or plateaus, biological windows of vulnerability, or social or ethnic vulnerability or exposure.

15.5.2 RESEARCH POLICY

ALS is a rare disease and an association, if real, might not translate into an absolute risk which was above *de minimis* bench marks for occupational exposures. A job-exposure matrix examining shocks, contact currents, and electric and magnetic fields with various summary exposure metrics might help resolve the shock vs. magnetic field explanations for ALS, if applied to the existing data bases. Clarity in this rare disease might have implications for more-common diseases associated with EMF exposures.